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Adjuvant alpha adrenergic blockers: Are they equally efficient for renal and upper ureteral calculi disintegrated by shock wave lithotripsy?

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Shock wave lithotripsy;
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Abstract

Objectives: To evaluate the effects of tamsulosin on stone clearance and analgesic requirements after shock wave lithotripsy (SWL) for solitary renal and upper ureteral calculi.

Patients and methods: A prospective randomized placebo controlled study was carried out on 126 patients who underwent SWL for solitary radio-opaque renal or upper ureteral calculi $\leq$20 mm. Patients were randomized into two groups receiving either 0.4 mg of tamsulosin (GT) or placebo (GP). SWL was performed 3-weekly until patients became stone-free or for a maximum of 3 months. Analgesics were used on demand and pain was evaluated by a visual pain scale.

Results: Renal stones represented 55.6% and 66.7% for GT and GP, respectively ($p = 0.27$). Mean renal and ureteral stone size were (12.3 ± 1.8 mm vs. 11.5 ± 2.3 mm, $p = 0.14$) and (9.7 ± 2.6 mm vs. 8.6 ± 1.7 mm, $p = 0.1$) for the GT and GP, respectively. GT required fewer SWL sessions for ureteral (1.2 vs. 1.6, $p = 0.02$) and renal stones (1.8 vs. 2.3, $p = 0.08$). Stone-free rate (SFR) was higher in GT for upper ureteral stones (96.4% vs. 66.7%, $p = 0.01$) and renal pelvis stones at a cutoff size >10 mm ($p = 0.01$). The mean time of stone clearance was significantly lower in GT (4.2 ± 1.9 weeks vs. 7.5 ± 2.3 weeks, $p = 0.001$) for ureteral stones. Attacks of renal colic were more frequent in GP (82.5% vs. 44.4%, $p = 0.04$) with increased demand for analgesia ($p = 0.04$). Steinstrasse was recorded in 3 and 7 patients of the GT and GP, respectively ($p = 0.32$).

Conclusion: Tamsulosin facilitates clearance of upper ureteral stone fragments after SWL and decreases the analgesic requirements. These effects were not similarly evident for renal stones.

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Introduction

Extracorporeal shock wave lithotripsy (SWL) has radically changed the management of urolithiasis and has become the least invasive treatment modality for renal and ureteral stones. The success of SWL can be optimized by careful patient selection, consideration of stone characteristics, and the alteration of treatment parameters [1]. After SWL, the migration of stone fragments is modulated by the sympathetic nervous system. It acts on ureteral smooth muscle which is dense in alpha-adrenergic receptors [2–4]. Medical therapy for stone clearance has gained increasing attention in the last years especially for the treatment of lower ureteral calculi. It has been suggested that the administration of alpha-adrenergic antagonists augments stone expulsion rates and reduces colic events [5]. These drugs are able to inhibit the basal sympathetic tone, decreasing the peristaltic frequency and dilating the ureteral lumen, thus facilitating stone passage [6]. This has encouraged the investigation of drugs for upper tract calculi which has shown promising results in terms of the facilitation of stone clearance, the reduction in colic attacks, as well as the decreased need for analgesic intake [7–10].

There is sparse literature [11–13] evaluating the role of adjuvant tamsulosin after SWL for renal stones. The aim of the present study was to compare the effect of adjuvant tamsulosin on renal and upper ureteral calculi disintegrated by SWL in terms of stone clearance and analgesic requirements and to detect factors that may affect the stone-free status.

Materials and methods

A prospective randomized placebo controlled study was carried out on 126 patients (72 males and 54 females) with single radio-opaque renal or upper ureteral stones ≤ 2 cm in largest diameter. Patients were blinded to whether they received treatment or placebo. There were 57 patients in each group to detect a difference in the success rate of 30%, with α of 0.05 (2-sided) and a power of 90%. Six (10%) patients were added to each group to make up for patient withdrawals throughout the study.

Exclusion criteria

Patients were excluded from the study if they had any of the following: age < 18 years, multiple stones, radiolucent stones, stones > 2 cm in largest diameter, previous SWL failure, history of spontaneous stone expulsion, urinary tract infection, distal obstruction, congenital renal or ureteral anomalies, serum creatinine $\geq$ 2 mg/dl, uncorrectable bleeding disorders, hypotension, morbid obesity or pregnancy, and concomitant use of calcium channel blockers, α-adrenergic antagonists, or corticosteroids.

Strategy of management

Patients were subjected to full history taking and clinical examination, as well as laboratory investigations including urinalysis with culture and sensitivity when indicated, blood chemistry and coagulation profile. Imaging studies performed included plain abdominal film (KUB), intravenous urography ± abdomino-pelvic ultrasonography (US). All patients were managed by SWL for stone disintegration using the electromagnetic Siemens Lithostar Lithotripter under fluoroscopic guidance with a shock rate of 90/min and an energy level of 14–15 kV. The procedure was terminated when stone disintegration was satisfactory or to a maximum of 4000 shock waves. SWL was repeated every 3 weeks until the patient became stone-free or for a maximum of 3 months. The patients were randomized into 2 equal groups, using a random number generator assisted by a computer program. Patients received either 0.4 mg tamsulosin (GT) or placebo (GP) once daily, started immediately after SWL and continued for a maximum of 3 months or until the patients became stone-free or an auxiliary procedure had been used. Sodium diclofenac was used as on-demand analgesia in the form of either 50 mg tablets per os or 75 mg ampoules injected intramuscularly.

All patients were evaluated bi-weekly by history taking, clinical examination and follow up KUB ± US to evaluate for the disintegration of the stone and the presence of obstruction. Success of SWL was represented by either well fragmented stones with a follow-up of 3 months or until the patient became stone-free (all fragments, except $\leq$3 mm non-obstructing gravel, completely cleared). To minimize inter-observer bias, all KUBs were evaluated by a team which consisted of two radiologists as well as the researcher. Patients with unfragmented stones, with residual fragments >3 mm, or those who required auxiliary procedures for obstruction were considered failures of SWL. Auxiliary procedures included placement of ureteral stent or percutaneous nephrostomy, ureteroscopy, or percutaneous nephrolithotomy. The frequency of colic or pain was evaluated by the visual analog scale for pain (from the least [1] to the most severe [10] pain) and the need for analgesia was evaluated by a specially scaled questionnaire, filled out by the patient at home and interpreted by the researcher at follow-up. The primary study end-points were the stone-free rate (SFR) and the factors that might affect it, while the secondary end-points were the time required for stone clearance, pain frequency and intensity, the incidence of steinstrasse, and the need for any auxiliary procedures.

Ethical considerations

All patients were informed about their condition and treatment options available for their stones, as well as the possible complications of SWL and side-effects of tamsulosin. All patients had sufficient time to ask questions and consider the study before providing informed consent to participate. All patients' data were kept confidential and reviewed only by the researcher. All sheets of the patients were coded by study identification number so that no unique patient identifying data were apparent.

Statistical analysis

Data were collected and tabulated using the Statistical Package for Social Science for Windows (SPSS, Chicago, IL) version 17. Descriptive statistics were presented in terms of percentage, frequency, mean and standard deviation. The differences in SFR between both groups and other categorical variables were analyzed with Fisher's exact test. Continuous variables were analyzed using Student's t-test. p-Values < 0.05 were accepted as statistically significant.

Results

All the patients completed the follow-up schedule. Table 1 shows the basic characteristics of both groups. There were no statistically significant differences between the groups in terms of gender, age, body mass index, stone size and stone location.

The GT patients required fewer SWL sessions to become stone-free (1.2 vs. 1.6, $p = 0.02$) and (1.8 vs. 2.3; $p = 0.08$) for ureteral and renal stones, respectively, even after controlling for the stone size ($p = 0.03$ and $p = 0.06$, respectively) (Table 2).

The overall SFR was 87.3% (55 of 63) in GT and 73% (46 of 63) in GP ($p = 0.59$). The upper ureteral stones managed by tamsulosin (GT) had significantly higher stone clearance when compared with GP (96.4% vs. 66.7%; $p = 0.01$), but there was no significant difference between the groups in terms of renal stone clearance (80%

Table 1 Characteristics of patients in tamsulosin and placebo groups.

Variables	GT No (%)	GP No (%)	p-Value
Male gender	44 (69.8)	39 (61.9)	0.45
Mean age ± SD (years)	52.8 ± 8.2	49.4 ± 11.3	0.06
Mean BMI (kg/m^2)	28.5 ± 5.3	27.1 ± 6.7	0.87
Stone size (mm)			
Renal	12.3 ± 1.8	11.5 ± 2.3	0.14
Ureteral	9.7 ± 2.6	8.6 ± 1.7	0.1
Renal stones	35 (55.6)	42 (66.7)	0.27
Upper calyx	5 (3.2)	4 (6.4)	1.00
Mid-calyx	3 (4.8)	6 (9.5)	0.49
Lower calyx	12 (33.3)	14 (28.6)	0.83
Pelvis	15 (14.3)	18 (22.2)	0.68
Upper ureteral stones	28 (44.4)	21 (33.3)	0.27
Total	63 (100)	63 (100)	NA

GT: tamsulosin group; GP: placebo group; BMI: body mass index.

vs. 76.2%; $p = 0.79$) (Table 2). However, at a renal stone size cut-off point >10 mm, SFR rate was significantly higher in renal pelvis stones of GT ($p = 0.01$).

The mean time of stone clearance was significantly lower in GT (4.2 ± 1.9 weeks vs. 7.5 ± 2.3 weeks, $p = 0.001$) for ureteral stones even after controlling for stone size ($p = 0.01$). However, renal stone clearance time was not significantly different between the groups (5.3 ± 1.2 weeks vs. 9.1 ± 1.9 weeks, $p = 0.10$) even after controlling for stone size ($p = 0.08$).

Attacks of renal colic were significantly more frequent in the GP (3.5 ± 1.9 vs. 2.4 ± 1.2, $p = 0.003$) with increased demand and doses for analgesia in GP ($p = 0.04$). Steinstrasse was recorded in 3 and 7 patients of the GT and GP, respectively ($p = 0.32$). In GT, all cases resolved spontaneously whereas 3 of 7 (42.8%; $p = 0.47$) patients in GP required auxiliary intervention for development of severe colic not responding to analgesia in 2 patients and obstructed kidney with fever in 1 patient. GP patients reported significantly greater mean (range) VAS scores than did GT patients (7 (3–10) vs. 4 (1–7), $p = 0.001$). SFR of renal calculi after SWL stratified by location is presented in Table 3. Five (8%) patients in GT reported minor side-effects in the form of intermittent headache and dizziness in 4 and prolonged diarrhea in 1 patient. These non-specific self-limited side-effects did not necessitate withdrawal of the drug. No similar side-effects were reported in the control group.

Table 2 The outcome of SWL in the tamsulosin and placebo groups.

Variables	GT	GP	p-Value
Stone-free rate			
Overall	87.3%	73%	0.59
Renal	80%	76.2%	0.79
Ureteral	96.4%	66.7%	0.01
Mean time of clearance (weeks)			
Renal	5.3 ± 1.2	9.1 ± 1.7	0.10
Ureteral	4.2 ± 1.7	7.5 ± 2.3	0.001
SWL sessions			
Renal	1.8	2.0	0.06
Ureteral	1.2	1.6	0.02
Mean colic attacks	2.4 ± 1.2	3.5 ± 1.9	0.003
Mean VAS scores	4 (1–7)	7 (3–10)	0.001

GT: tamsulosin group; GP: placebo group; VAS: visual analog scale.

Table 3 Stone-free rate of renal calculi after SWL stratified by stone location.

Variables	GT No (%)	GP No (%)	p-Value
Upper calyx	4 (80)	4 (100)	1.00
Mid-calyx	3 (100)	4 (75)	0.50
Lower calyx	7 (58.3)	9 (64.3)	1.00
Pelvis	14 (93.3)	15 (83.3)	0.61
Total	28/35 (80.0)	32/42 (76.2)	0.79

GT: tamsulosin group; GP: placebo group.

Discussion

SWL has become the primary treatment for patients with uncomplicated urolithiasis, even with the refinement of current endourological methods for stone removal [11]. There is no doubt regarding the ability of powerful lithotripters to break renal calculi into small fragments. Therefore, the SFR is highly dependent on other parameters, such as the ability of the ureter to transport the fragments. The ureteral wall contains densely populated smooth muscle cells with α-adrenergic receptors, especially in the distal third of the ureter. Receptor blockade inhibits basal smooth muscle tone and hyper-peristaltic uncoordinated frequency whilst maintaining tonic propulsive contraction [14], thus dilating the ureteral lumen and facilitating stone passage. Recently, new treatments have been developed aiming to further improve the success rate after SWL. A pooled analysis of 16 studies using α-antagonists in patients with distal ureteral stones suggested that the addition of these agents significantly improved spontaneous stone expulsion [9]. Zhu and colleagues performed a meta-analysis study to determine the role of adjuvant α-blockers after SWL [15]. The authors concluded that although there is some evidence for the benefits of tamsulosin after SWL, a high-quality confirmatory trial is warranted before final clinical recommendations can be made.

Many recent trials reinforced the role of α-blockers and specifically tamsulosin as adjuvant therapy for upper urinary calculi disintegrated by SWL in terms of increased stone clearance, decreasing the frequency and severity of colic together with reducing the dose and frequency of analgesia [7–10]. However, in evaluating the role of tamsulosin after SWL for renal stones, the conclusion is not clear at this stage due to there being only three published studies [11–13]. The criteria of success in all these trials included residual stones <4 mm, i.e. not complete stone-free status. Gravina et al. [11] reported a significantly higher clinical success rate at 3 months in those who received tamsulosin (78.5% vs. 60%, $p = 0.037$) and this became more significant for those with a stone size larger than 10 mm. Colic occurred less frequently in the tamsulosin group (26.1% vs. 76.9%; $p = 0.001$). These results are comparable with those of the present series. The relatively lower figures of the former trial may be the result of being a controlled, no-treatment study which included only patients with renal stones. The authors had enrolled patients with stones located in the renal pelvis or middle and upper pole calices and 58% (75/130) of them were in the renal pelvis.

Naja et al. [12] reached the same conclusion in their open-label randomized study. Although being statistically insignificant, the overall success rate at 3 months was higher in the tamsulosin group (94.1% vs. 84.6%; $p = 0.14$). There was no significant difference between the groups in terms of steinstrasse and auxiliary procedures used. The authors lost 24% of patients in the tamsulosin arm to follow-up and 78% (90/116) of their patients had renal pelvis stones. None of the previous two studies had any patients with lower pole calyceal stones.

Recently, a randomized study evaluating tamsulosin after SWL of renal stones reported a better clearance rate (73% vs. 55%; $p = 0.008$), significantly lower number of colic attacks and less analgesia requirements in the tamsulosin arm [13]. However, more than 60% of the 186 patients had renal pelvis stones, whereas lower calyceal stones constituted only 13% of the patients. Moreover, the power of that study and the sample size were not calculated to give reliable results, especially with up to 15% of patients in the tamsulosin arm being lost to follow-up. Nevertheless, the clearance rate of lower calyceal stones showed no significant differences between the groups, which indicate the impact of stone location on the SFR.

In the present series, the SFR with tamsulosin treatment after SWL for renal stones was not significantly greater compared with the placebo group. However, it was more effective in patients who had upper ureteral stones (96.4% vs. 66.7%, $p = 0.01$). The cause of this difference remains unclear, as each renal stone will become a ureteral one during its washout journey after SWL. This might be related to a selective role of α-blockers for the ureteral wall that contains abundant receptors. Moreover, it seems that other factors may affect these figures, such as the relatively high proportion of lower pole renal stones in the present series.

Lower pole stone washout after SWL is different from other stone locations due to anatomical considerations that prevent stone fragments to be cleared efficiently [16]. To date, the role of adjuvant α-blockers has not been conclusively evaluated in lower pole stone clearance. This necessitates further randomized prospective trials with proper sample size to investigate this issue.

Patients receiving tamsulosin in the present trial were found to have a lower chance to develop steinstrasse after SWL, and if they did, the steinstrasse would resolve spontaneously before developing complications, as was previously reported [9]. Rasim et al. found that tamsulosin used after SWL was beneficial in terms of reducing the number of ureteral colic episodes and the severity of pain in the patients who developed steinstrasse. However, the resolution rates were not significantly different between the study groups [14].

Ng et al. found that SFR after SWL for renal stones was significantly lower in patients older than 40 years [17]. However, in the current cohort, SFR for proximal ureteral stones was higher in GT patients who were older than the placebo group (53 years vs. 49 years, $p = 0.06$). This may indicate a favorable effect of tamsulosin on stone clearance after SWL for upper ureteral stones, which requires further evaluation.

There are several confounding factors that could possibly affect the comparison of such trials. These include variability of demographic data and stone characteristics, e.g. size and location. However, these differences could be accepted provided there was a comparison between two groups managed by the same lithotripter.

There were no serious side-effects reported by patients treated with tamsulosin and there were no indications to stop the drug in any patient. The reported side-effects of the drug were non-specific and self-limiting, such as headache, dizziness and diarrhea. All side-effects were controlled with symptomatic treatment and did not necessitate discontinuation of the drug.

This study has two main limitations. Firstly, SFR was evaluated by KUB which might miss a fragment in up to 13% of patients [18]. Routine postoperative computerized tomography was not done so as to not deviate from the standard care used in practice, as well as avoiding the increased radiation exposure. Secondly, the lower number of renal stones distributed over four different renal locations necessitate further evaluation to reach a reliable clinical conclusion.

Conclusion

Tamsulosin seems to improve the outcome of SWL for upper ureteral calculi in terms of stone clearance and decreased analgesic requirements. These effects were not evident for renal stones. A high quality confirmatory trial is warranted to evaluate the role of adjuvant therapy after SWL for renal calculi, especially lower pole calyceal stones.

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